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Meloxicam usage in cats, and its potential adverse effects on the renal function

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1. Introduction

Meloxicam is a frequently encountered non-steroid anti-inflammatory drug (NSAID) in feline medicine. It is used to control postoperative pain and inflammation in cats, associated with orthopedic procedures, ovariohysterectomy and other soft tissue surgeries. NSAIDs are popular drugs in veterinary medicine because of their easy application, dual analgesic and anti-inflammatory properties and minimal effect on the pet's behaviour. Their use in feline medicine is markedly less compared to canines. NSAIDs are used on a regular basis to control both chronic and acute pain in dogs. Its limited use in cats is due to their increased sensitivity to NSAID toxicity. This increased sensitivity is mainly due to a reduced capacity to metabolize the drug through hepatic glucuronidation (Maddison, 2007). As meloxicam act through an oxidative pathway rather than the glucoronidation pathway, the drug could be suitable for use in cats. The safety concerns related to use of meloxicam in cats is chiefly related to renal side effects. Meloxicam act through inhibition of the cyclooxigenase (COX) pathway, and is a COX-2 selective NSAID. This selectivity gains a COX-1 sparing effect, which has been developed to get a higher safety margin. Even though it spares COX-1, a significantly higher number of side effects are reported in meloxicam treated cats due to nephrotoxicity (European Medicines Agency CVMP assessment report, 2010). This increased incidence of renal side effects may have several explanations, but could possible be due to an interspecies difference in the renal expression of the COX-1 and COX-2 isoforms in the kidney (Khan *et al.*, 1998).

The higher incidence of adverse reactions in cats using NSAIDs has resulted in differences regarding authorization between continents. Metacam (Boehringer Ingelheim Vetmedica) is a product licensed for cats containing meloxicam. It is authorized by the European medicine agency as an injection (5 mg/ml or 2 mg/ml) and an oral suspension (0.5 mg/ml), to control and relive acute and chronic pain in cats (EPAR, 2012). In the United States of America, FDA (U.S. food and drug administration) only approved Metacam solution for injection as a one-time only subcutaneous injection prior to surgery in 2004. The FDA does not authorize the oral suspension for use in cats. Based on a review of reported drug related adverse events for Metacam in cats, FDA recognized a high number of cases of acute renal failure and death. This was after repeated use of meloxicam in cats. In 2010 FDA asked the manufacture; Boehringer Ingelheim Vetmedica, Inc., to add an additional boxed warning; "Warning:

repeated use of meloxicam has been associated with acute renal failure and death. Do not administer additional doses of injectable or oral meloxicam to cats." (FDA, October 27 2010).

The limited authorization of NSAID for use in cats makes control of feline pain more difficult. Cats do not demonstrate pain-associated behavior as well as dogs do, and there are not as many authorized analgesic drugs for them. In addition veterinarians are more cautious to prescribe analgesic drugs as opoids and NSAIDs to cats due to their increased risk of adverse reactions. This results in higher incidences of undertreated cases of pain in feline patients. In a Canadian study, it was discovered that an estimated 6000 dogs and cats undergoing ovariohysterectomy monthly did not have appropriate pain relief (Hewson *et al.*, 2006). Poor pain management will have a negative effect on animal welfare, but also affect physiological processes resulting in a stress response, poor tissue healing and an increased energy requirement.

Does the difference in the authorization between Europe and the United States indicate that repeated use of meloxicam increases the risk of acute renal failure in cats? Is the overall risk subjective, or could it be justified by looking at quantitative data. Will a one-time only subcutaneous injection of meloxicam prior to surgery provide enough postoperative pain relief for cats undergoing ovariohystectomy, or do they require additional analgesia in the postoperative period? This paper discusses the use of NSAIDs, and deals with the pharmacokinetic and pharmacodynamic properties of meloxicam in cats. It examines the use of meloxicam as an analgesic and anti-inflammatory agent for cats undergoing routine neutering, and discuss if repeated use of meloxicam increases the risk of acute renal failure. The goal is to better understand the unique physiology of drug metabolism in cats, and how we can improve pain management using NSAIDs in feline patients.

2. Non-steroidal anti-inflammatory drugs

The non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that act through inhibition of the arachidonic acid pathway and thereby the prostaglandin synthesis. They have analgesic, anti-inflammatory and antipyretic properties (Blood *et al.*, 2007). NSAIDs mechanism of action is by inhibition of the cyclooxygenase (COX) enzyme in various tissues, and thereby reduction of the synthesis of prostaglandins from arachidonic acid. The COX enzymes are present in two distinct isoforms, COX-1 and COX-2. Both enzymes are

important in regulating physiological processes such as renal blood flow, gastrointestinal mucosal protection and blood clotting. But especially COX-1 that are a constitutive enzyme produced in most tissues. COX-2 plays a considerable role in pathological processes as in inflammation and neoplasia, and is chiefly an inducible enzyme (Lascelles *et al.,* 2007). By knowing the different tissue distribution of the two COX isomers, pharmaceutical companies have developed NSAIDs that have the ability to inhibit the COX isoforms selectively. By sparing COX-1 inhibition, and being COX-2 selective we can gain fewer incidences of reduction of the homeostatic functions, and less adverse reactions (Sparkes *et al.,* 2010). How selective or sparing an NSAID are on the different isoforms is depending on their COX-1/COX-2 ratio. The ratio is assessed by estimating the IC_{50} of the drug, which is defined as the concentration of the NSAID needed to inhibit the enzyme activity with 50%. To gain a drug with high COX-2 selectivity, a high ratio is desirable, in other words; the COX-2 isoform is inhibited at lower drug concentration than COX-1. We could classify the different NSAIDS based on this knowledge: a drug with COX-1/COX-2 ratio of less than 1 would be COX-1 selective. If the drug has a ratio over 1 this drug is COX-2 preferential, a ratio that exceeds 100 classifies the NSAID as a COX-2 selective drug (Fox, 2007). We can gain 3.groups of NSAIDs if we classify each group based on its COX-1/COX-2 ratio (Table 1).

Table 1: Classification of NSAIDs based on the COX-1/COX-2 inhibition ratio

Categories	NSAIDs
1.group (non-selective COX inhibitors)	aspirin, ketoprofen, phenylbutazone, metamizole, flunixin, paracetamol, diclofenac
2.group (more selective COX-2 inhibitors)	carprofen, meloxicam, nimesulide
3.group (selective COX-2 inhibitors)	coxibs

Its important to note that the COX-1/COX-2 ratio is species specific, and the isoforms can exert different roles in tissues in different species involved. It is therefore essential to have knowledge about the different tissue distributions, and be aware of the COX selectivity when choosing a NSAID (Lascelles *et al.,* 2007). Based on this knowledge it is impossible to evaluate the potency and efficacy of different NSAIDs in the cat when looking at on results from other species (Giraudel *et al.*, 2005). The COX-selectivity of different NSAIDs in cats is still under study, but Lees, *et al.* did an experiment with cats using whole blood assay after

meloxicam and carprofen treatment to determine the COX-1 and COX-2 selectivity. Their discovery was that meloxicam and carprofen have a similar efficiency for COX-2 inhibition, but that meloxicam is more potent as a COX-1 inhibitor when we compare the IC_{50} values obtained. Based on this their conclusion was that meloxicam is a COX-2 preferential, and carprofen as COX-2 selective NSAID (Lees *et al.*, 2004). Further studies are now being done to assure adequate knowledge about the COX selectivity and distribution.

Even though COX-2 is mainly considered as an inducible enzyme chiefly present in inflammatory cells, studies have proven that by using COX-2 selective NSAIDs we could still experience adverse reactions such as acute renal failure, tromboembolic diseases and gastrointestinal ulceration (Coruzzi *et al.,* 2007; Harris, 2002). This is demonstrated by the fact that the COX-2 enzyme is present also as a constitutive enzyme in these tissues, and plays an important role in the kidney by preserving renal perfusion during hypovolemia (Sparkes *et al.,* 2010).

Flower and Vane (1972) discovered a third COX isomer from brain homogenate using acetaminophen, this has been described as the COX-3 enzyme. This discovery purposed a target for centrally acting NSAIDs. In 2002 Chandrasekharan *et al.*, described COX-3 rather as a variant of COX-1, and not as an own isomer. They examined RNA from canine cerebral cortex and discovered that the COX-3 enzyme derives from the same gene as COX-1. They also proved that acetaminophen, diclofenac and dipyrone all inhibited COX-3 at a higher range than COX-1 and COX-2. These are NSAIDs with low anti-inflammatory activity, and high analgesic and antipyretic action. As COX-3 originates from the same gene as COX-1, these findings may suggest that the COX-1 enzyme has a fundamental role in fever and/or pain. (Chandrasekharan *et al.*, 2002). Yet this centrally acting COX-3 enzyme is only proven as a treatment method against pain in dogs where other NSAIDs are not suitable (Papich, 2008).

In addition to COX enzymes, NSAIDs may directly or indirectly interfere with other enzyme pathways. The 5-lipooxygenase (5-LOX) produces leukotrienes that can be gastrotoxic and proinflammatory. This pathway is especially activated in cases where COX-inhibition leads to accumulation of arachidonic acid (Alvaro-Gracia, 2004). Some novel NSAIDs have been developed to have dual inhibition of both COX and 5-LOX to provide increased

gastrointestinal safety, but there are no approved studies to support the use of these new NSAIDs in cats (Lascelles *et al.,* 2007).

2.1 Gastrointestinal side effects

NSAIDs produce a gastrotoxic effect by their inhibition of the prostaglandin synthesis (systemic effect), but also through a local pathway. Prostaglandins are important in the production of the mucus layer that protect, and prevents gastric ulceration. The local effect act by inducing direct cellular injury, and it is due to ion trapping within the gastric mucosa. The ion trapping happens because NSAIDs are slightly acetic drugs (Khan and McLean, 2012). Gastric ulceration, vomiting and diarrhoea are frequently reported side effects in case of many NSAIDs. But the gastrointestinal adverse reactions are seen more frequently in NSAIDs with low selectivity, which have a higher COX-1 inhibition. (Sparkes *et al.*, 2010). Anyway, the risk of gastric ulceration is always higher when applying an NSAID when the animal is dehydration, in hypovolaemic shock, has reduced gastric perfusion or is on concurrent corticosteroid therapy (Maddison, 2007).

2.2 Renal side effects

PGE_2 and PGI_2 are important renal protecting agents in case of systemic vasoconstriction. They act by inducing vasodilatation in the afferent arteriole, and thereby maintain the renal blood flow (Khan and McLean, 2012). Prostaglandins produced by both COX-1 and COX-2 is important in maintaining renal perfusion, especially during phases of potential ischemia. They also regulate salt and water balance, in addition to renin secretion (Jones and Budsberg, 2000). The potential nephrotoxic effect of NSAIDs is particularly relevant in hypovolemic or hypotensive circumstances, which can occur after trauma, dehydration or during anaesthesia (Lascelles *et al.,* 2007). Khan *et al.* (1998) described the renal expression of COX-1 and 2, and demonstrated that both isoforms are constitutively expressed and important in maintaining physiological renal function. In dogs and rats COX-2 is the main enzyme activated in the macula densa and the thick ascending limb of loop of Henle in case of hypovolemia. When COX-2 is activated it leads to an increased concentration of renin in the blood. The same condition does not result in COX-1 expression in these species. (Khan *et al.,* 1998; Jones and Budsberg, 2000).

2.3 Haemostatic abnormalities

NSAIDs can affect the platelets and vascular endothelium, and thereby cause disturbances in haemostasis. Platelet aggregation is dependent on formation of thromboxane A_2 from

arachidonic acid. This is a COX-1 depended reaction, and can be inhibited by certain types of NSAIDs. This delayed platelet activation can increase the risk of bleeding and cause haemorrhage. On the other hand can a highly COX-2 selective NSAID increase the risk of intravascular trombosis. The vascular endothelium produces prostacyclin by the help of COX-2, which protects against intravascular initiation of the clotting process (Jones and Budsberg, 2000; Lascelles *et al*, 2007).

3. NSAIDs and cats

NSAIDs are an important class of drugs in feline medicine, but there are some unique differences regarding the pharmacokinetic and pharmacodynamic properties of the drugs in cats. The pharmacokinetic properties of NSAIDs are of major importance since cats have deficient pathways in the metabolism of the drugs compared to other species (Maddison, 2007). Metabolism of many NSAIDs is through the liver, by hepatic glucuronidation. The bile and/or the kidney then excrete the secondary metabolites (Lascelles *et al.,* 2007). Since cats express low capacity of hepatic UDP-glucuroninosyltransferase (UGT) isoforms, they are at increased risk of toxicity due to the prolonged duration of effect, and risk of drug accumulation. Especially from the phenol containing drugs as acetaminophen (Paracetamol) toxicity is well documented (Robertson, 2008). Within the group of salicylates, acetylsalicylic acid (aspirin) depends on the conjugation with glucoronic acid or glycin for its metabolism, which in turn leads to a prolonged elimination half-life in cats and also potential toxicity (Brander *et al.*, 1991). On the other hand, other NSAIDs as meloxicam and piroxicam are metabolized by oxidation and have an elimination half-life of 15 hours (Metacam label information) and 12 hours (Heeb, *et al.*, 2003) respectively, which is reduced in comparison with the dog. Ketoprofen is another NSAID that are licensed for cats, and highly depends on thioesterification. Cats have similar elimination half-life of ketoprofen as the dog (Lascelles *et al.,* 2007).

Even though cats are at increased risk for NSAID toxicity, this class of drug remains important in multimodal pain management in feline patients. NSAIDs are used both to control acute and chronic pain, associated with surgeries and musculoskeletal conditions. Controlling pain in cats is crucial both on a physiological and emotional level. Pain will have a negative consequence on the welfare of the animal, its connection with its owner, and it will also delay recovery and healing after trauma/surgery (Sparkes *et al.*, 2010). Pain will generally decrease

the appetite of the patient, and this can delay wound healing, and might lead to decreased immunity that increases the risk of postoperative complications (Robertson and Taylor, 2003). To achieve an efficient analgesic protocol, especially in the postoperative period we should aim to target the different parts in the pain perception pathway. To achieve this, a combination using opoids, NSAIDs, ketamine and an alpha-2 agonist seem to gives a maximal postoperative analgesia. When dealing with postoperative pain, it is important that we start analgesic treatment preoperatively to prevent "wind-up", which will cause a severe post-operative pain and delay recovery time. Pre-emptive analgesia will also give a safer anaesthetic protocol, because we can reduce the dose of the anaesthetic agents (Robertson and Taylor, 2003). Also long-term use of NSAIDs is an important tool to improve the condition of cats with chronic painful disorders, especially diseases as osteoarthritis. But at current date, meloxicam is the only licensed drug for long-term application for cats in Europe. With an initial dose of 0.1 mg/kg, and maintenance dose of 0.05 mg/kg/day. It is important to note that the drug should always be used at lowest effective dose to avoid adverse reactions (Robertson, 2008). Other licensed NSAIDs in cats include; carprofen, ketoprofen, robenacoxib and tolfenamic acid (Iff, 2011).

3.1 Carprofen

Carprofen is licensed for use in cats as a once subcutaneous or intravenous injection (4 mg/kg) in Europe (Iff, 2011). It is grouped as a preferential COX-2 inhibitor, and when administered at the licensed dose (4 mg/kg) it have 100% inhibition of COX-2, and 44% inhibition of COX-1 (Giraudel *et al*., 2005). Its main fields of usage are as an analgesic agent to control postoperative pain. Lacelles *et al*. (1995) and Balmer *et al*. (1998) both described Carprofen as an efficient analgesic agent for cats undergoing ovariohysterectomy. In dogs it is also licensed to control chronic painful conditions as osteoarthritis and degenerative joint diseases. Carprofen has both analgesic and anti-inflammatory properties, and in addition an antipyretic effect (Ramsey, 2011). Its efficiency compared to other licensed NSAIDs in cats was assessed in a study comparing carprofen, meloxicam, ketoprofen and tolfenamic acid in cats undergoing ovariohysterectomy. The experiment investigated analgesic efficiency of the different agents by using the VAS pain score, and by considering wound tenderness. As conclusion all four agents provided equally good postoperative analgesia after ovariohysterectomy (Slingsby and Waterman-Pearson, 2000). Possible side effects connected with carprofen injection are mainly gastrointestinal (Ramsey, 2011). Lascelles *et al*.(1995) measured urea and creatinin levels after carprofen administration, and it did not seem to cause

any adverse reaction on kidney function. The half-life of carprofen is estimated to 20 hours, and the agent provides good postoperative analgesia for approximately 24 hours (Robertson and Taylor, 2003).

3.2 Ketoprofen

Ketoprofen is licensed for use in cats in Europe as an injection subcutaneously, and can be followed by oral application. The approved dose is 2 mg/kg subcutaneously, given daily up to 3 days. Alternatively an injection can be followed by oral administration of the drug up to 5 days, at 1 mg/kg (Iff, 2011; Lascelles *et al.,* 2007). Ketoprofen is also licensed for use in cats in Australia and Canada, but its not approved for feline patients in USA. The COX-1/COX-2 ration in still not been well established, and no data have been published about the COX inhibition in the cat (Lascelles *et al.,* 2007). Ketoprofen have analgesic, anti-inflammatory and antipyretic properties. In 1996 Glew *et al.*, investigated the antipyretic effect by administering it together with antibiotics in cats with clinical pyrexia. Ketoprofen proved to have a good antipyretic effect that lasted between 8-24 hours. Its analgesic properties when used postoperatively after ovariohysterectomy, is equally efficient as the other licensed NSAIDs for cats (Slingsby and Waterman-Pearson, 2000). Its potential toxicity is similar to other NSAIDs, and Lees *et al*. (2003) detected that it has an inhibition of thromboxane synthesis lasting 72 hours, after administration of 2 mg/kg.

3.3. Robenacoxib

Robenacoxib is a COX-2 selective NSAID licensed for both cats and dogs. It is licensed for use in cats as a single subcutaneous injection peri- or postoperatively, at a dose of 2 mg/kg. Or as 6 mg tablets, administered up to 6 days. The oral preparation is not licensed to follow the injection in cats (Ramsey, 2011). Robenacoxib belong to the coxib class of NSAIDs, together with deracoxib and firocoxib. The two latter are not approved or licensed for use in feline patients (Lascelles *et al.,* 2007). Giraudel *et al*. (2009), and Schmid *et al*. (2010) have classified robenacoxib as COX-2 selective NSAID. In an in vitro study the IC_{50} COX-1/COX-2 ratio was determined as 32.2 in cats. The coxib class of NSAIDs are known for their COX-2 selectivity, and thereby considered as a safer drug with fewer adverse reactions related to the gastrointestinal tract and blood clotting (Schmid *et al*., 2010). Robenacoxib (2 mg/kg subcutaneous injection) was evaluated as superior to control postoperative pain after surgery compared to meloxicam. It was also judged as a safe agent for cats when administered preoperatively (Kamata *et al*., 2012).

3.4 Tolfenamic acid

In the class of NSAIDs tolfenamic acid belong to the fenmate group (Lascelles *et al.,* 2007). The drug inhibits cyclooxygenase enzyme, but it is also believed to act as an antagonist on prostaglandin receptors, and thereby inhibit prostaglandin synthesis directly. The COX-1/COX-2 ratio is not defined with certainty in the cat (Ramsey, 2011). Tolfenamic acid is licensed for use in felines in Europe, Canada, Australia and New Zealand, but not in the United States (Lascelles *et al.,* 2007). It is labelled at a dose of 4 mg/kg as a subcutaneous injection, which can be repeated after 24 hours, once. Per oral application can follow the injection for maximum 3 days, at a dose of 4 mg/kg. Regular dosing of tolfenamic acid is not advised (Ramsey, 2011; Iff, 2011). It is used to relive inflammation and pain, and it is also used to treat respiratory disorders in cats. Tolfenamic acid furthermore has an antipyretic action, and can be applied as a symptomatic treatment in febrile conditions (Ramsey, 2011; Lascelles *et al.,* 2007). The drug is licensed for treatment of febrile conditions, and as auxiliary agent in therapy of upper respiratory tract disorders in the cat (Sparkes *et al.,* 2010). In a study comparing tolfenamic acid and meloxicam, both provided reduced wound tenderness postoperatively in cats undergoing ovariohysterectomy (Benito-de-la-Víbora *et al.,* 2008). Slingsby and Waterman-Pearson in 2000 also found Tolfenamic acid equally efficient as meloxicam, ketoprofen and carprofen, as a postoperative analgesic agent.

4. Meloxicam and cats

Meloxicam is a COX-2 preferential NSAID, labelled for cats as Metacam, Loxicom and others. It exists as an injectable solution with two different concentrations; 2 mg/ml and 5 mg/ml (Ramsey, 2011). The injection is indicated as a perioperative injection to control postoperative pain after orthopaedic surgery, ovariohysterectomy or castrations. The licensed dose is 0.3 mg/kg as a single subcutaneous injection (Boehringer Ingelheim Vetmedica Inc., 2010). Meloxicam (Metacam, Boehringer Ingelheim Vetmedica) is authorized by the European medicines agency, for usage in cats both as an injection and as an oral suspension. The oral suspension licensed for cats has a concentration of 0.5 mg/ml. It can be used together with an initial injectable dose (0.2 mg/kg subcutaneously) to control postoperative pain, up to 5 days with a dosage of 0.05 mg/kg *per os*, starting 24 hours after the injection. If used to control chronic pain, the initial dose is labeled as 0.1 mg/kg *per os* once. Then the dosage should be reduced to 0.05 mg/kg *per os* repeated every 24 hours (Ramsey, 2011). The FDA (U.S. food and drug administration) does not approve the oral suspension for use in cats, and

meloxicam is only licensed as a single subcutaneous injection in the United States. The different authorizations of meloxicam use for cats, in Europe and The United States are given in Table 2.

Table 2: License of meloxicam in Europe and The United States (Ramsey, 2011; Boehringer Ingelheim Vetmedica Inc., 2010):

Use	Europe			United States		
	Dosage	Concentration	Number of doses	Dosage	Concentration	Number of doses
Postoperative pain / inflammation	0.3 mg/kg sc.	2 mg/ml 5 mg/ml	Once	0.3 mg/kg sc.	5 mg/ml	Once
	0.2 mg/kg sc.	2 mg/ml	Repeated 5 days with oral suspension (0.5 mg/ml) at 0.05 mg/kg *per os*			
Chronic pain	0.1 mg/kg *per os*	0.5 mg/ml	Repeated at 0.5 mg/kg *per os*	Not licensed for repeated use		

sc.: subcutaneous

4.1 Pharmacokinetic/pharmacodynamic properties of meloxicam in the cat

When evaluating the pharmacokinetic (PK) and pharmacodynamic (PD) properties of NSAIDs it is important to assess the target species of interest. This is essential because metabolism and action of NSAIDs have high interspecies variations. Evaluation of PK and PD parameters of a drug is a prerequisite to ensure a safe and accurate dosage in clinical situations. It is important to take into consideration the model, the markers and the species when interpreting PK/PD parameters and results, to accurately evaluate the NSAIDs action and response (Lees *et al.*, 2004).

4.1.1 Pharmacokinetics

Pharmacokinetic properties of meloxicam (Metacam) injection 5 mg/ml, was summarized in a report published by FDA October 2004, sponsored by Boehringer Ingelheim Vetmedica. The bioavailability of meloxicam was studied in 8 cats by intravenous, subcutaneous and oral administration of the drug. The injections were with 5 mg/ml Metacam solution, and the oral application was with 1.5 mg/ml Metacam oral suspension. A single dose of 0.3 mg/kg

meloxicam was applied, and blood samples collected 0, 5, 1, 3, 6, 10, 24, 48, 72 and 120 hours after drug administration. The study showed that the subcutaneous injection of meloxicam had 100% bioavailability, and the oral administration had 80%, which justifies that the drug can be used by subcutaneous and oral applications. NSAIDs are weak acids and lipid soluble, the unionized form in low pH makes them easily absorbable by the gastric cells, and in the upper small intestine (Khan and McLean, 2012). Maximal mean plasma concentration (1.1 µg/ml) is reached after 1.5 hours after a subcutaneous injection, and 3 hours after oral drug intake (EPAR, 2012). When distributed within the body, approximately 97% of meloxicam is bound to plasma proteins (FDA NADA 141-219, 2004). Meloxicam is distributed at a volume of 0.09 l/kg in cats (EPAR, 2012). In a study performed by Grudé *et al*. (2010), no conjugated metabolites was detected after oral administration of meloxicam ($[^{14}C]$ meloxicam), proving that it is metabolized in a phase-I oxidative reaction without any conjugation. This is beneficial for feline use, since the cat has reduced capacity of hepatic glucoronidation. The excretion of meloxicam in cat was demonstrated to be mainly fecal, with 79 % elimination, and the remaining 21 % was eliminated in the urine (Grundé *et al*., 2010). Meloxicam (5 mg/ml, 0.3 mg/kg) has an elimination half-life ($T_{1/2}$) of approximately 14-16 hours in the cat (EPAR, 2012).

4.1.2 Pharmacodynamics

Meloxicam act through inhibition of the cyclooxygenase enzyme pathway, and thereby inhibit the production of prostaglandins. Meloxicam is classified as a COX-2 preferential NSAID in the cat (Sparkes *et al.*, 2010). In an in vitro experiment meloxicam was compared to carprofen for COX-1 and COX-2 inhibition using whole blood assay. At IC_{50} values both NSAIDs had similar potency for COX-2 inhibition, 1.35 µmol for meloxicam and 1.14 µmol for S (+) carprofen. But meloxicam exhibit a higher COX-1 inhibition than S (+) carprofen (4.10 µmol, and 29.1 µmol respectively). In a clinical situation, minimal 80% of COX-2 inhibition is required, so evaluating IC_{80} values is more relevant. When 80% of COX-2 is inhibited, correspondingly 40% and 5 % COX-1 is inhibited in meloxicam and S (+) carprofen respectively. This concludes that meloxicam is not a COX-2 selective agent, but is classified as a COX-2 preferential drug, while carprofen is grouped as COX-2 selective in the cat (Lees *et al.*, 2004; Giraudel *et al.*, 2005).

4.1.3 Efficacy

Meloxicam belong to the oxicam class, and have antipyretic, analgesic and anti-inflammatory properties. The efficiency of meloxicam in the cat has been studied with regards to different

aspects of its properties. Slingsby and Waterman-Pearson investigated the analgesic effect of meloxicam as an agent to relive postoperative pain in 2000. They compared the efficiency of carprofen, ketoprofen, meloxicam and tolfenamic acid to control postoperative pain, in cats undergoing ovariohysterectomy. Forty female cats were admitted to the study, and visual analogue scale (VAS) was used to evaluate postoperative analgesia. The NSAIDs where administered as a once injection at extubation. All agents where evaluated as equally efficient to relive postoperative pain, and only one cat in each group of tolfenamic acid, ketoprofen and meloxicam required rescue analgesia. Another study examining the analgesic efficiency of meloxicam was done on 139 cats undergoing oncychectomy and/or neutering. The analgesic effect was compared to cats treated with butorphanol. Of the 139 cats 72 received meloxicam as an analgesic agent. The agent was administered as a single subcutaneous injection prior to surgery (meloxicam: 0.3 mg/kg, butorphanol: 0.4 mg/kg). Analgesic efficiency was evaluated based on palpation, gait score and visual observation. The meloxicam treated cats had lower pain scores, were less lame and fewer cats required rescue analgesia compared to the butorphanol group (Carroll *et al*., 2005).

Meloxicam can also be used in combinations with opioids to relive postoperative pain. The combination provides the early peak effect of the opioid together with the prolonged duration of effect with NSAIDs, which results in superior effect compared to using one of the agents alone (Steagall *et al*., 2009). In a study performed by Polson *et al*. (2012), meloxicam in combination with buprenorphine or butorphanol was compared to carprofen in the same combination. One hundred client-owned cats were admitted to ovariohysterectomy, and all where under midazolam-medetomidine-ketamine anesthesia. Postoperative pain was scored using a simple descriptive scale (SDS) from 0 (no pain) to 4 (clear pain). No cats received a higher pain score than 2, and there was no difference between the meloxicam-buprenorphine/butorphanol or carprofen-buprenorphine/butorphanol combinations. It should also be noted, that the anesthetic agents medetomidine and ketamine have analgesic properties that further contribute to the postoperative analgesia. The study demonstrated that using multimodal analgesia protocols with meloxicam provide excellent postoperative pain control in cats undergoing ovariohysterectomy (Polson *et al*., 2012). A single injection with meloxicam (0.2 mg/kg) provides postoperative analgesia for approximately 18-24 hours (Slingsby and Waterman-Pearson, 2002; Robertson and Taylor, 2003).

Meloxicam is the only NSAID licensed by the European medicines agency for control of chronic pain in cats. Metacam 0.5 mg/ml oral suspension is licensed starting with an initial dose of 0.1 mg/kg, and 0.05 mg/kg daily as maintenance dose (EPAR, 2012). The efficacy of repeated administration of meloxicam has been studied in several research programs. In a trial consisting of forty cats diagnosed with osteoarthritis, meloxicam was administered at a dosage of 0.01-0.03 mg/kg daily and the cats was evaluated after 1 month. Based on owner and veterinary assessment (discontinuous scales), the treatment was rated as excellent by 85% of the owners and 80% of the veterinarians (Gunew *et al.*, 2008). Carroll *et al.* (2011) demonstrated that oral meloxicam suspension given at a maintenance level of 0.025 mg/kg daily have good efficiency in cats. The experiment was done using urate injected into the stifle joint, to achieve a feline arthritis model. When meloxicam (Metacam) is used for chronic relief of musculoskeletal pain, a steady-state concentration is reached after 1 day when the licensed dose (0.1 mg/kg first day, and maintenance dose of 0.05 mg/kg daily) is applied (Lehr *et al*., 2009). At the licensed dose Metacam 0.5 mg/ml oral suspension was concluded to be efficacious and safe for cats with chronic musculoskeletal disorders, in the Metacam European Public Assessment Report (EPAR), scientific discussion (2010).

Meloxicam (Metacam, Boehringer Ingelheim Vetmedica) is an efficient antipyretic agent in cats. A feline endotoxin model proved that a dose of 0.3 mg/kg meloxicam (5 mg/ml) reduced fever in twelve cats injected with endotoxins. The dose response between 0.3 mg/kg and 0.5 mg/kg was not significant, which justifies the labelled dose of 0.3 mg/kg (Justus and Quirke, 1995). Another feline endotoxin model used 0.6 mg/kg meloxicam in 6 cats, and compared the antipyretic effect to a placebo group. The meloxicam group had a lower average body temperature compared to the placebo group with 1.7 degree, demonstrating that meloxicam is a potent antipyretic agent in the cat (EPAR, 2010). Meloxicam is also proven as an efficient anti-inflammatory agent. The efficacy and potency was studied in a cat model using subcutaneous injection of kaolin in a cat paw, and meloxicam (5 mg/ml) at a dose of 0.3 mg/kg. The meloxicam treated cats had lower lameness score, body temperature and skin temperature compared to the control group (Giraudel *et al.*, 2005).

4.2 Targeting animal safety in the use of meloxicam (Metacam) in the cat

Meloxicam is labelled for feline patients, but care should be taken for animals that suffer from gastrointestinal, cardiac, renal or blood clotting disorders. Also meloxicam should not be administered to hypovolemic, dehydrated or hypotensive induviduals. Pregnant or lactating

cats, and kittens less than 6 weeks should not receive meloxicam (Ramsey, 2011; EPAR, 2012). Typical adverse reaction connected to NSAID toxicity is reported with meloxicam, including gastrointestinal side effects, renal failure and hepatic toxicity (EPAR, 2012). Meloxicam should not be administered together with glucocorticoids, potentially nephrotoxic drugs or together with other NSAIDs (Boehringer Ingelheim Vetmedica Inc., 2010). In addition, due to the high protein binding of meloxicam (97%) care should be taken when administered together with other protein binding drugs. Drugs competing for the same binding sites may affect each other, depending on the affinity for the receptors (Khan and McLean, 2012).

Meloxicam is labelled under the brand Metacam (Boehringer Ingelheim Vetmedica) for use in cats, and the difference between continents within the authorization of the product is connected to the potential adverse reactions of meloxicam in cats. In the United States Metacam is licensed as a once only subcutaneous injection prior to surgery. The label information for Metacam (meloxicam) 5 mg/ml solution for injection, have since 27th October 2007 contained an additional box warning: "Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats" (Boehringer Ingelheim Vetmedica Inc., 2010). This additional box warning is based on FDA's review of reported adverse drug events for the product. FDA has identified cases of renal failure and death in cats associated with repeated use of Metacam (meloxicam) in cats. As mentioned earlier Metacam is licensed for repeated use in Europe, with both the injectable solution (5 mg/ml, and 2 mg/ml) and the oral suspension (0.5 mg/ml) (EPAR, 2012). Does difference in the authorization between Europe and USA indicate that repeated use of Metcam (meloxicam) increases the risk of acute renal failure in cats? Is the overall risk subjective, or could it be justified by comparing quantitative data?

4.2.1 Nephrotoxicity

Different processes can explain the adverse effects of NSAIDs on the kidney in different species. Hypovolemia, dehydration or hypotension are all mechanisms which leads to increased risk of decreased renal perfusion, and meloxicam administration should be avoided in patients which are under these conditions (EPAR, 2012). Another suspected cause of the toxicity is the different expression of cyclooxygenase-2 enzyme in the renal parenchyma. PGE_2 and PGI_2 are both important prostaglandins produced in the renal tubules and the glomeruli respectively. Which cyclooxygenase enzyme (COX-1/COX-2) that regulates these

prostaglandins are species dependent in case of the kidney. As mentioned earlier, COX-2 is mainly an inducible enzyme activated by pathological processes in the body, but scientists have now discovered that COX-2 also acts as a constitutive enzyme in the kidney of some species. This might explain the species variations in the NSAID induced nephrotoxicity (Jones and Budsberg, 2000; Goodman *et al.*, 2009). Meloxicam is a COX-2 preferential NSAID, which in a clinical condition when 80% of COX-2 is inhibited, a 40 % COX-1 inhibition will occur (Giraudel *et al.*, 2005). As meloxicam inhibits COX-2 preferably over COX-1 the nephrotoxic effect could be explained if cats possesses a higher proportion of constitutive COX-2 enzyme in the kidney. But to the authors knowledge no study evaluating the COX distribution in the feline kidney have been published.

A study to evaluate the effect of meloxicam on the glomerular filtration rate (GFR) was conducted by Goodman *et al.* (2009). The experiment was carried out on 6 healthy, euvolemic and conscious cats. Meloxicam was administered at 0.2 mg/kg per oral the first day, and at 0.1 mg/kg from day 2-5. Iohexol was given together with subcutaneous fluid. The iohexol clearance was measured on day 0 and 5. The study concluded that meloxicam did not alter the GFR in conscious, euvolemic cats (Goodman *et al.*, 2009). Since this experiment was conducted on euvolemic, conscious cats the results cannot be compared to the effect of meloxicam on GFR in cats that does not fulfill the same requirements. It has been shown that while prostaglandins are important in maintaining the renal perfusion under hypotension or hypovolemia, their effect is neglectable under normal, physiological conditions (Jones and Budsberg, 2000). This underlines the importance of a well hydrated, normotensive state when we administering meloxicam to cats.

4.2.2 Suspected adverse reactions (SARs) reports

The committee for medicinal products for veterinary use (CVMP) made a report based on the suspected adverse reactions (SAR) in connection with use of the oral suspension of Metacam (1.5 mg/ml and 0.5 mg/ml) all over the world. The report covers the time period 1.1.2003-15.10.2006, and thereby the time period before meloxicam oral suspension was authorized in Europe. The report therefore includes the adverse reactions in connection with off label use of meloxicam in cats. The basis of the report originates from the safety concerns by the FDA for off label use of meloxicam in cats in the United States. CVMP reported incidences of 624 adverse reactions, of a total of 162 339 234 treated cats with oral Meloxicam suspension (Table 3). This results in a frequency of 0.00038% SARs worldwide. Of the 624 cases, 145

were reported fatal (0.00009%). Only 36 of the SARs was reported from Europe, while the remaining 588 was from non-EU/EEA countries. 87% of the SARs were reported from USA, and it should be noted that only 22% of the total sale of Metacam were from the United States (European Medicines Agency CVMP assessment report, 2006).

Table 3: Data from: European Medicines Agency CVMP assessment report, 2006:

	Total number of treated animals	Suspected adverse reactions		Fatal cases	
EU/EEA	100 842 383	36		16	
Non EU/EEA	61 496 851	588		129	
Total	162 339 234	624	0.00038%	145	0.00009%

The reported doses administered in connection with the SARs shows that adverse reactions already occurred on an oral dose of 0.05 mg/kg (97 cases). The majority of the adverse reactions were connected to a dose between 0.11-0.29 mg/kg (174 cases). The most common adverse reaction was related to the kidneys and urinary tract, with 356 cases, of them renal failure was the most frequent. The second most frequent reported SARs were gastrointestinal disorders (152 cases), and also systemic disorders like anorexia (61 cases) and lethargy (67 cases). The systemic disorders could also be related to both the gastrointestinal side effects and renal failure. The report was based on an assumption that 10% of the sales volume of Metacam oral suspension for dogs was used off label in cats. The uncertainty of the background of the SARs should also be considered, since additional effects like anesthesia, hypovolemia, lacking fluid therapy during surgery have not been taken into consideration (European Medicines Agency CVMP assessment report, 2006).

A new CVMP assessment report was made in 2010. This report covers the time period 01.05.2007 to 30.04.2010, and includes both Metacam (meloxicam) 5 mg/ml solution for injection, and Metacam (meloxicam) 0.5 mg/ml oral suspension for cats. During this period 560 cats treated with Metcam 5 mg/ml solution for injection had reported adverse reactions. 59 of these were reported to be in connection with Metacam oral suspension (0.5 mg/ml). The most common adverse reactions reported in connection with 5 mg/ml suspension for injections in cats was renal and urinary tract disorders, with 341 cases. 218 cats had digestive tract disorders, with emesis as the most frequent complaint. Death or euthanasia was reported in 198 cats (European Medicines Agency CVMP assessment report, 2010).
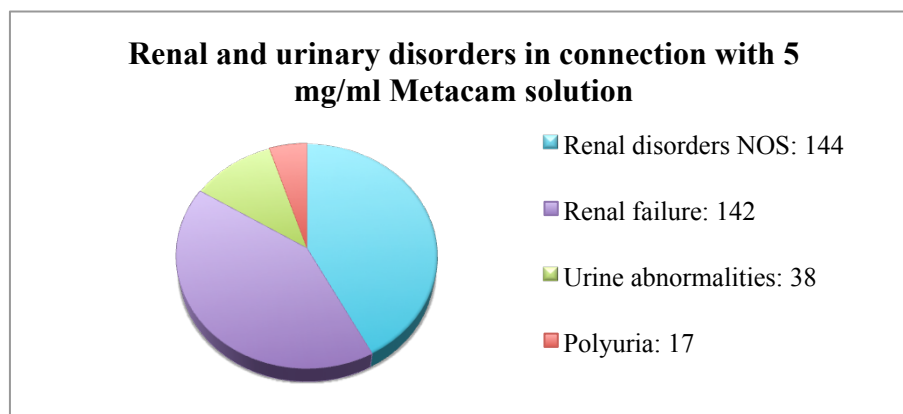
Figure 1: Number of renal and urinary disorders in connection with 5 mg/ml meloxicam injection, from European Medicines Agency CVMP assessment report, 2010

Suspected adverse reactions in connection with Metacam 0.5 mg/ml oral suspension for cats was reported in 152 feline patients. The product had been used according to label in 41 cases. The incidence of the reported cases is 0.0053%, if you take into account that one bottle was used for one cat. Of the reported adverse reactions the most common was digestive tract disorders with 68 cases. 26 cats died or were euthanized, and 54 cats suffered from renal and urinary tract disorders, including 14 cases of renal failure (European Medicines Agency CVMP assessment report, 2010).
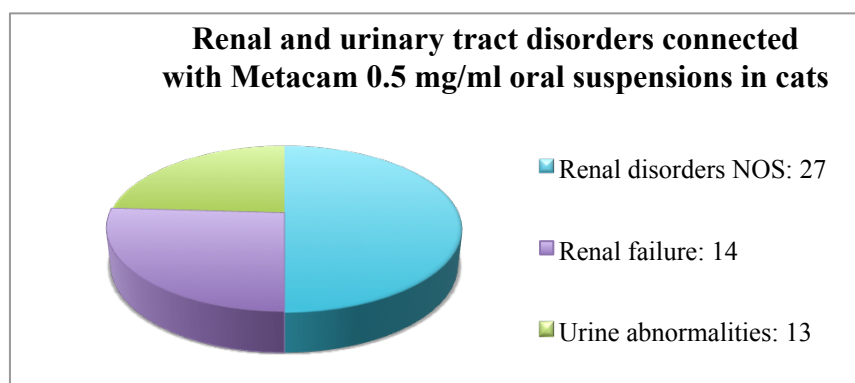

Figure 2: Number of renal and urinary disorders in connection with 0.5 mg/ml meloxicam oral suspension, from European Medicines Agency CVMP assessment report, 2010

Based on the frequency of reported adverse reactions in cats the market authorization holder (Boehringer Ingelheim Vetmedica Inc.) was asked to add to the label that renal disorders are more frequently observed in cats than in dogs in connection with usage of Metacam 5 mg/ml solution for injection and Metcam 0.5 mg/ml oral suspension for cats (European Medicines Agency CVMP assessment report, 2010).

The FDA (U.S. food and drug administration) has made a summary on all adverse drug experiences covering the time period from 01.01.1987 to 30.04.2013 (Table 4). The additional box warning added on Metacam 5 mg/ml solution for injection for cats in 2007, is based on FDAs review of the adverse events in connection with repeated use of meloxicam in cats. Their ADE report revealed that cats had high number of kidney and urinary abnormalities, and cases of death. The report does not take into account any underlying disease, or simultaneous use of other drugs. In addition the report does not take into consideration if the drug was used according to label or off label.

Table 4: The 10 most common reported adverse drug experiences (ADE) reported in connection with different routes of administration (FDA, ADE report 1987 – 2013):

ADE, oral meloxicam	Times reported	ADE, parenteral meloxicam	Times reported	ADE, unknown route, meloxicam	Times reported
High K$^+$, blood	71	Death	72	Anorexia	13
Ataxia	65	Dehydration	71	Depression/lethargy	11
High kidney values, blood	**64**	Anemia	68	**High creatinine, blood**	**9**
Adipsia	54	Low spesific gravity, urine	65	Death	9
High ALT, blood	54	Weight loss	49	**Kidney failure**	**8**
Polyuria	48	High K$^+$, blood	43	**High BUN, blood**	**7**
Convulsions	47	Polydipsia	34	Vomiting	7
High WBC, blood	46	Adipsia	24	Death (euthanized)	4
Blood, urine	42	Blood, urine	24	Dehydration	4
High bilirubin, blood	40	**High kidney values, blood**	**22**	**Azotemia**	**3**

ALT: Alanine transferase, WBC: white blood cells, BUN: blood urea nitrogen, ADE: adverse drug experiences

4.2.3 Tolerance studies

To get more information regarding the target animal safety, in connection with both renal and other side effects, tolerance studies have been performed. A study was done evaluating the possible adverse reactions in connection with repeated use of Meloxicam at 0.3 mg/kg or 0.6 mg/kg for 9 succeeding days. The cats did initially receive a subcutaneous administration of either 0.3 or 0.6 mg/kg meloxicam, with follow up treatment of the same dose in an oral form.

12 adult cats were admitted to the study. Two cats from both the 0.3 mg/kg and 0.6 mg/kg dosage group died during the experiment. After 9 days, all cats showed clinical signs indicating NSAID toxicity, and the experiment revealed that repeated use of meloxicam at a dosage of 0.3 mg/kg and 0.6 mg/kg caused pyloric and duodenal ulceration, and cannot be regarded as safe. The conclusion was that a dosage reduction is required (EPAR, 2010). A new study evaluating the safety after a dose reduction was done under the same conditions as above. Four cats received an initial subcutaneous dose of 0.3 mg/kg, followed by oral administration of 0.1 mg/kg meloxicam. The other group of four cats got one subcutaneous injection of 0.6 mg/kg meloxicam at day one, then 0.2 mg/kg the upcoming 8 days. Only one cat developed duodenal ulceration, some sensitive cats showed depressed behavior. On pathological examination, inflammation of the gastrointestinal mucosa could be detected. The conclusion was that even at reduced dosage, repeated use of meloxicam should be used with caution, and the drug has a narrow therapeutic index in the cat (EPAR, 2010).

A target animal safety study performed by Vanessa A. Redgrave was done to determine possible side effects by repeated subcutaneous injection of Metacam (meloxicam) 5 mg/ml solution. The cats were divided into three groups receiving 0.3 mg/kg, 0.9 mg/kg and 1.5 mg/kg for 3 consecutive days. Infiltration of inflammatory cells in the gastrointestinal mucosa was observed in all treatment groups, but erosions were only detected in cats that got 0.9 mg/kg and 1.5 mg/kg. Two of the cats in the group receiving 1.5 mg/kg daily had increase in blood urea nitrogen value and creatinine. At necropsy, cats from the group receiving 0.9 mg/kg and 1.5 mg/kg had detectable pathological changes. Lesions found were fibrosis of the bowman capsule, dilation and necrosis of the cortical tubules, interstitial inflammatory cell infiltration and interstitial fibrosis. The conclusion of the study was that 0.3 mg/kg Metacam (meloxicam) 5 mg/ml was tolerated clinically for 3 days. While a 3 or 5 times increase in dosage is associated with several adverse reactions (FDA NADA 141-219, 2004).

Carroll *et al*. (2005) compared meloxicam and butorphanol in an experiment to evaluate the safety and efficiency when administered prior to surgery. They found elevated blood urea nitrogen (BUN) in cats treated with meloxicam. The drugs were administered once prior to surgery, meloxicam at a dosage of 0.3 mg/kg (5 mg/ml solution). Six cats (8,3%) in the meloxicam group had postoperative elevated BUN outside the reference range. Of these six cats, three also had elevation of creatinine, but the values were within the physiological range. No cats in the butorphanol treatment group had any elevation of BUN or creatinine.

An investigation was done in New Zealand based on the theory that acute renal failure (ARF) is connected with NSAID toxicity in cats undergoing neutering. Sixteen cats undergoing neutering (10 males and 6 females) experienced ARF in connection with NSAID used prior to surgery. Of these, seven received meloxicam. None of the cats had fluid therapy or proper blood pressure measurement during the surgery, and none had preoperative blood and urine analysis done. The conclusion of the study was that cats are of increased risk of intrinsic acute renal failure during neutering when NSAIDs are used, especially if the above-mentioned conditions are not provided (Robson *et al*., 2005).

In an experiment evaluating the safety and efficacy of 3 and 5 days treatment with meloxicam, a 0.2 mg/kg subcutaneous injection was given initially before onychectomy or sterilization. Thereafter treatment was continued with an oral dosage of 0.05 mg/kg for 3 or 5 days. No cats experienced blood urea nitrogen or creatinine values out of the reference range, and there were no reported gastrointestinal adverse reactions detected. This study proves that if meloxicam is used preoperatively according to the licensed dose (EPAR, 2012), with good anesthetic monitoring and fluid therapy, no clinical significant renal toxicity should be experienced (Ingwersen *et al*., 2012).

Since meloxicam (Metacam oral suspension; Boehringer Ingelheim Vetmedica) is the only agent that is licensed for chronic use in cats by the European medicine agency, the tolerance of this application is regarded as good, and the risk of possible detrimental effect on the kidneys is low. A long-term study evaluates the safety and efficacy of meloxicam as a treatment for cats with osteoarthritis. The cats received meloxicam (1.5 mg/ml) at an initial dose of 0.1 mg/kg, with maintenance dosage ranging from 0.01 to 0.03 mg/kg. The study concluded that meloxicam could be considered safe as a chronic analgesic agent for cats with osteoarthritis. There were no significantly higher incidences of disease in the meloxicam treated cats compared to the control group. Furthermore, the incidence of renal disease and the measured creatinine values did not show significant differences between the groups (Gunew *et al*., 2008). At the licensed dose 0.05 mg/kg meloxicam (Metacam oral suspension 0.5 mg/ml), daily administration did not produce any adverse reactions in a long-term study in healthy cats (Dammgen, 2007).

Existing renal disease is currently listed as a contraindication for use of meloxicam in cats (Boehringer Ingelheim Vetmedica Inc., 2010). But a recent study evaluates the effect of meloxicam on cats already suffering from chronic renal failure (CRF). Thirty-eight cats over 7 years with degenerative joint disease were admitted to the study. Twenty-two of the cats had existing CRF (renal group), while 16 had normal kidney values (non-renal group). The cats received meloxicam at a maintenance dose of 0.02 mg/kg for 327 and 467 days in the non-renal group and renal group respectively. Their results were compared to two control groups, not receiving meloxicam, but that fit the same standards as above. After the treatment period, there were no difference between the non-renal group and the control group. And the cats of the renal group had less progression of their chronic renal disease compared to the control group. Their conclusion was that chronic use of meloxicam in cats with existing CRF could be used safely at a maintenance dose of 0.02 mg/kg (Gowan *et al*., 2011).

5. The use of meloxicam in cats, and its potential adverse effects on the renal function, in cats undergoing ovariohysterectomy

Meloxicam is a frequently used NSAID in feline medicine to control postoperative pain. The intention of this study was to determine if meloxicam affects the kidney values (blood urea nitrogen, and creatinine) in any degree, after one single subcutaneous injection of meloxicam prior to ovariohysterectomy. The study focuses on the use of pre-operative administration of meloxicam due to the increased risk of decreased physiological regulation of homeostasis. During anesthesia there is an increased risk of NSAID toxicity, as there is difficulties to maintain a normotensive, and sometimes euvolemic state. The goal of the study was to examine if there were any potential side effects affecting the kidney in cats that are under anesthetic influence.

5.1 Material and methods

5.1.1 Animals
9 client-owned cats where accepted to the study. The cats were admitted to the clinic for routine ovariohysterectomy during the summer 2012. All owners signed a consent form prior to admission. The cats were between 3 months to 3 years old. Prior to inclusion, all cats were examined and made sure that they were healthy. Hearth rate, rectal temperature and capillary refill time was checked in addition to the hydration status. Only cats that fit into the ASA 1 or

2, and had not received any NSAIDs for the last 30 days where admitted for the project. Their mean body weight was 2.34 kg. All cats had one biochemical analysis before surgery, to check that renal values were within the physiological range. Mainly blood urea nitrogen (BUN), creatinine, calcium and phosphorous was measured, but also ALP and ALT was taken into consideration.

5.1.2 Medication

All cats received *Zoletil vet. mixture* (0.1 ml/kg) intra muscularly, *Synulox vet.* (8.75 mg/kg) subcutaneous, and *Metacam vet* (meloxicam) 5 mg/ml solution for subcutaneous injection. One single injection of Metacam, at a dose of 0.3 mg/kg was given 10 minutes prior to the operation. No inhalation anesthesia or fluid therapy where used during the surgery. No analgesic agents were provided for the cats postoperatively.

5.1.3 Surgical procedure

All cats underwent ovariohysterectomy with a midline approach. An ovarioectomy hook was used to locate the ovaries and the uterus. One ligature was placed around the ovarian artery and vein together with the suspensory ligament, and another ligature made just cranial to the cervix, both with absorbable suture material (Vicryl). The incision wound was closed with 3 layers, using absorbable suture material. The abdominal musculature with simple interrupted sutures, the subcutaneous tissue sutured with simple continuous technique and the skin was closed with intradermal sutures. No cats experienced any complications during the surgery, and no pathological conditions of the uterus or any pregnancy was detected. Average time for the whole procedure was 25 minutes.

5.1.4 Postoperative period

Cats where kept in individual cages, and evaluated 2-3 hours after surgery for discomfort or other clinical signs related to renal side effects and postoperative complications. The analgesia was evaluated using a numerical rating scale (NRS)[1] with scores from 0-10, were 0 is no pain, 5 moderate pain and 10 worst possible pain. For pain assessment the posture, position in the cage, pupil size and response to wound palpation was evaluated. They were initially evaluated from the outside of the cage, and then eventually lifted and the wound was palpated. All cats got a protective body on after the surgery to prevent surgical wound injury. The cats were sent home after 4 hours, and owners were informed to look for typical signs related to NSAID toxicity, behavioral changes, and drinking and urination frequencies.

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[1] See appendix 9.1

5.1.5 Biochemical analysis

Two blood samples were collected from each cat. First a pre-enrollment blood analysis, to select cats suitable for the study. And 1-3 days postoperatively a control blood analysis was done, and compared to the preoperative result. Blood was drawn from *vena cephalica* or *vena jugularis*. Blood urea, creatinine, calcium and phosphorous were evaluated. Blood was collected from the vein into a vacutainer containing Li-Heparin. The sample was analyzed within 30 minutes with Rotor comprehensive diagnostic (Vetscan, Abaxis) at the clinic. The analysis includes results for albumin (ALB), alkaline phosphatase (ALP), alanine transferase (ALT), amylase (AMY), total bilirubin (TBIL), blood urea nitrogen (BUN), calcium (CA), phosphate (PHOS), creatinine (CRE), glucose (GLU), sodium (NA+), potassium (K+), total protein (TP), and globulin (GLOB).

5.1.6 Staging the renal disease

The renal safety was assessed according to IRIS (International renal interest society). The IRIS staging system is mainly used to diagnose chronic renal failure. But the system has also been adapted to stage acute kidney insufficiency (AKI). The AKI stage system has 5 grades, where each grade presents a proceeding of the acute kidney failure (Table 5). This is the main difference between the systems, since the staging of chronic renal failure is diagnosing the disease at a steady state. Evaluating the kidney damage by an AKI system gives us the opportunity to interfere with the process before the acute kidney damage becomes irreversible. By using the serum creatinine concentration we are able to diagnose subclinical conditions, even in cases where the creatinine concentrations are within the normal range. Animals that have an increase over $27\mu mol/L$ in creatinine within the non-azotemic range, during a 48 hour time interval, are classified as IRIS AKI stage 1. These animals may regain adequate renal function within 2 to 5 days if the initiating factor is removed. If the condition is not recognized and treated, or the initiating factor is not removed, the renal disease will progress to grade II-IV, and eventually become clinically apparent. Each grade is also evaluated based on urine production, and the response to fluid therapy. A positive responsiveness is an increase in the production of urine after 6 hours, to more than 1 ml/kg/hour, and/or decrease in the creatinine measurement. The advantage of this system is that we can diagnose and treat renal diseases earlier, and prevent acute renal failure (Baxter, 2012; Cowgill, 2012).

Table 5: Staging acute kidney injury according to Dr. Larry D. Cowgill, 2012

AKI stage	Serum creatinine (µmol/L)	Clinical findings
I	< 141	**Non-azotemic AKI** - Progressive increase in serum creatinine with > 27µmol/L within the last 48 hours - Diagnosed AKI: history, clinical signs, laboratory, diagnostic imaging, volume responsiveness, supporting evidence of AKI - Measured oligouria (<1 ml/kg/hour) or anuria > 6 hours
II	150-221	**Mild AKI** - Diagnosed AKI, static or progressive azotemia. - Progressive azotemic increase in serum creatinine (within 48 hours), or volume responsiveness - Measured oligouria (<1 ml/kg/hour) or anuria > 6 hours
III	230-442	**Moderate to severe AKI**
IV	450-884	Diagnosed AKI, increasing azotemia and functional renal failure.
V	>884	

AKI: Acute kidney insufficiency

5.1.7 Statistical analysis

All values for continuous variables are given as mean and 95% confidence interval, unless else stated. The potential differences between preoperative and postoperative creatinine and blood urea was analysed using GraphPad Prism version 6 (GraphPad Software, Inc. www.graphpad.com). Probabilities of less than 5% were considered statistically insignificant.

5.2 Results

The study was done to evaluate both the safety and the efficacy of one subcutaneous injection with 0.3 mg/kg meloxicam, administered prior to surgery. All 9 cats admitted completed the study. One cat had to be re-operated due to a surgical wound rupture.

The statistical analysis[2] revealed that there was no significant difference between the preoperative and postoperative creatinine and blood urea nitrogen values in the study group. The mean value for preoperative creatinine measurement was 89.11 µmol/L (75.7-102.5µmol/L), and postoperatively an identical mean creatinine value was found in the subjects with a slightly wider but not significantly different confidence interval (71.8-106.4 µmol/L). Blood urea nitrogen (BUN) had a mean value preoperatively of 8.27 µmol/L (6.95-

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[2] See appendix 9.2

9.58μmol/L). The postoperative BUN measurement had a mean value of 7.65 μmol/L (6.74-8.57μmol/L) (Figure 3a, 3b).
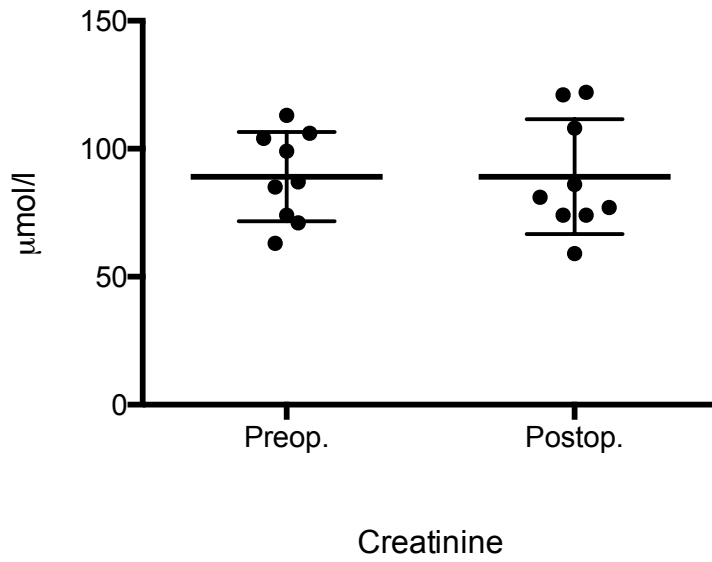

Figure 3a: Creatinine values preoperatively and postoperatively (Mean value and 95% confidence interval).
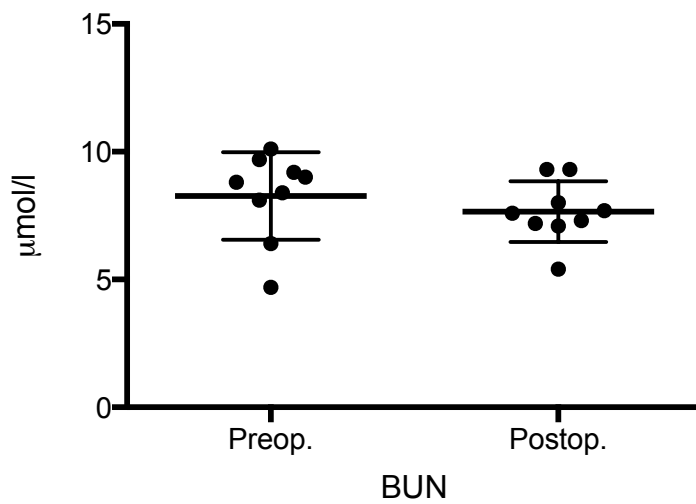

Figure 3b: Blood urea nitrogen (BUN) values preoperatively and postoperatively (Mean value and 95% confidence interval).

5.2.1 Safety

The 0.3 mg/kg dosage of meloxicam (5 mg/ml) administered once subcutaneously was tolerated well clinically among the 9 cats. None of the cats developed clinical signs of renal insufficiency or gastrointestinal side effects. Abdominal palpation of all cats reviled no change in kidney shape and size. The safety was evaluated based on the biochemical analysis, manly considering the renal parameters. Creatinine was measured, and all cats where within the physiological range (27-186 μmol/L). Only one cat classified into IRIS AKI stage 1, with a 34 μmol/L increase in serum creatinine between the two blood samples. This cat did not show any clinical signs for renal insufficiency. Four cats had an increase in the creatinine concentration, but lower than 27μmol/L, and did not classify as AKI cases. The blood urea nitrogen (BUN) measurement showed that four cats had increased BUN at the second blood sample, but results where within the physiological values (3.6-10.7 μmol/L) in all 9 cats. Calcium and phosphorous where elevated in some cats above the physiological range. This elevation could be indicative for renal disease, but can also be connected with other metabolic and/or endocrine processes. The elevation of calcium or phosphorous in these cats were considered less important, and not connected with the administration of meloxicam. Alkaline phosphatase (ALP) was higher than the physiological range (10-90 IU/L) in 5 cats, but all these cats where below 1 year old. Elevated ALP could be normal in growing animals, and not indicative of disease. Alanine aminotransferase (ALT) is a liver specific enzyme in cats, and elevation indicates hepatocellular damage. This enzyme was elevated in one cat (121 IU/L). No gastrointestinal side effects were noted.

5.2.2 Efficacy

The analgesic efficacy was evaluated at the clinic and at home by the owners. Analgesic effect was measured by using a NRS score, focusing on posture, position in cage, pupil size and wound tenderness. At home, owners had to evaluate behavioral changes, look for signs of distress, and appetite, drinking and urination frequencies. All cats, except three, showed signs of post-operative discomfort 2-3 hours after surgery. The average NRS score among the cats 2-3 hours postoperatively was 3, which may indicate that one single injection of meloxicam prior to surgery is insufficient for proper post-operative analgesia. Two cats where slightly lethargic and had episodes of inappetence at home. Urination and drinking was reported as normal in all cats. The average NRS score 1-3 days after the ovariohysterectomy was 1 (Figure 4).
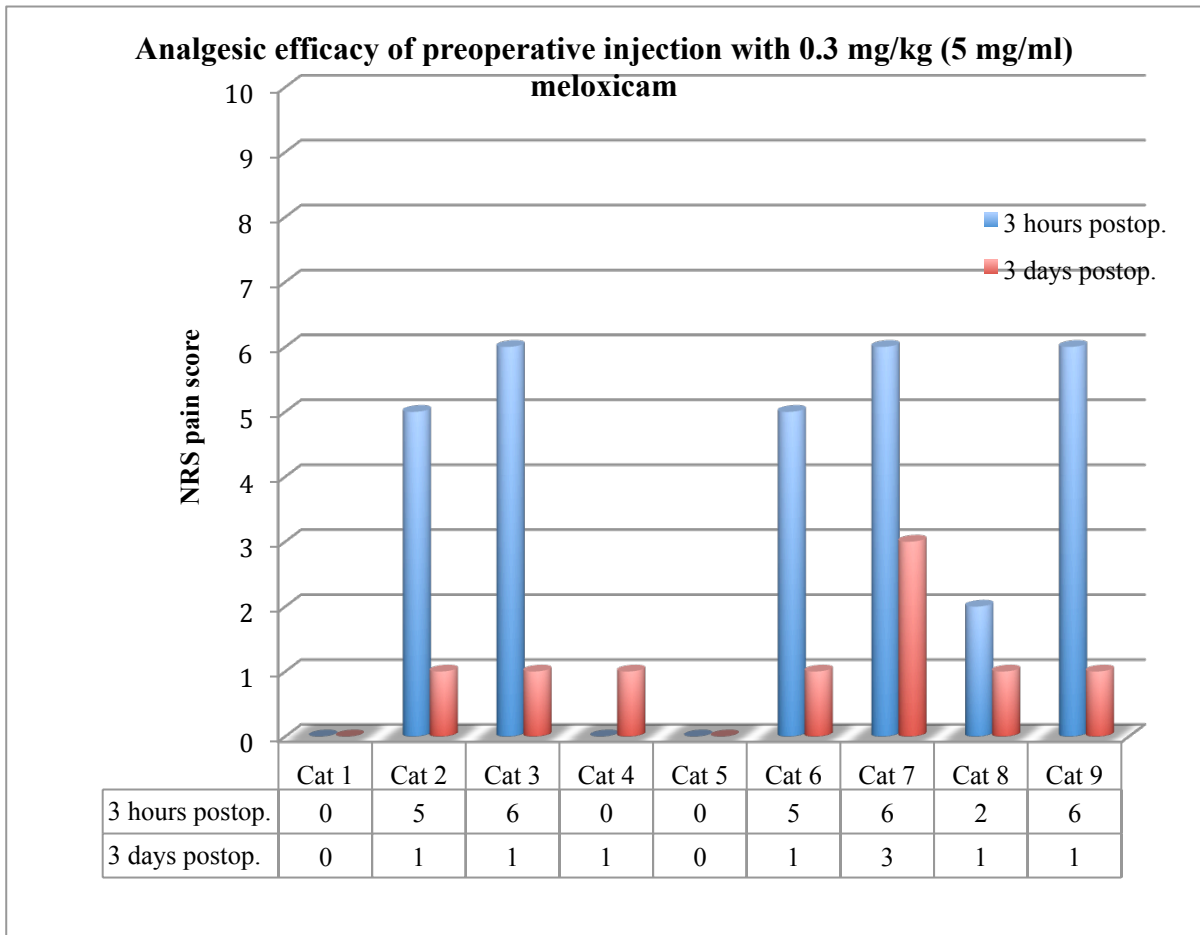
Figure 4: Analgesic efficacy of meloxicam at 0.3 mg/kg (5 mg/ml) administered prior to ovariohysterectomy.

6. Discussion

The aim of this study was to evaluate if one pre-operative injection with meloxicam would affect the renal function, and increase the risk of acute renal failure. The conclusion supports the findings of earlier research papers, that one single injection of Metacam (meloxicam) at 0.3 mg/kg with 5 mg/ml concentration, could be considered safe in cats undergoing ovariohysterectomy. To be proven safe to use, it is important to assure that the cat is healthy (ASA 1 or 2), well hydrated, and does not have any underlying renal or gastrointestinal disorders. It should also be taken into consideration that none of the cats admitted to the study received fluid therapy before or during the surgical procedure, which would further increase the risk of renal damage. As one cat classified into the IRIS AKI 1 system, the therapeutic index should be considered narrow and renal adverse reactions could occur. The limitations of this study are a small sample size, lack of placebo group and individual variations in keeping conditions at home. On the other hand, the study might provide some clinical relevance, as it

mirrors clinical situations. The analgesic potential of one single injection of meloxicam without additional postoperative administration was evaluated as less satisfactory with an average NRS score of 3. Limitation of the NRS scoring system is that it only gives a subjective measurement of discomfort. Also application of a body to protect the wound could give false positive as some cats could react by rolling and showing signs of distress. The NRS classification is originally adapted to humans which are able to tell on a scale 0-10, about level of discomfort. A Glasgow composite pain scale could be more useful for this study. Based on the statistical analysis, there was no significant difference between the preoperative and postoperative values of neither creatinine nor urea. As a conclusion the study should be regarded negative, but could be used as a clinical reference.

The licensing of meloxicam for use in cats is highly debated due to its narrow therapeutic index, mostly with concern for the renal safety. To this date, the distribution of COX isomers in the feline kidney, and the real impact of meloxicam on the renal physiology in cats are still under investigation. Khan *et al* (1998), Jones and Budsberg (2000) and Goodman *et al.* (2009) have stated the importance of COX-2 to support renal physiology during periods of hypovolemia or hypotension. The COX-2 selective inhibition by meloxicam could therefore play an important role in cases of acute renal failure following its administration. Especially in periods were the normal renal perfusion is suppressed. It is also important to consider that when meloxicam is administered with 80 % inhibition of COX-2, a 40% inhibition of COX-1 will happen simultaneously (Giraudel *et al.*, 2005). A dual inhibition of both COX isomers to this degree would further decrease the homeostatic balance, and increase risk of adverse effects. It is important to assure that the patient is normovoloemic, normotensive and does not have any renal or gastrointestinal disease before administrating meloxicam. Proven by Goodman *et al.* (2009), meloxicam does not affect the glomerular filtration rate in healthy, euvolemic and conscious cats. During anesthesia a normotensive state is generally hard to achieve as most anasthetic agents causes slight hypotension and reduced blood pressure. Careful patient selection, close monitoring of blood pressure and fluid therapy during anesthesia should all be criteria when administrating meloxicam before surgery (Ingwersen *et al.*, 2012). In clinical trials without proper monitoring or blood and urine analysis, acute renal failure have been experienced in association with preoperative meloxicam administration to cats undergoing neutering (Robson *et al.*, 2005).

To minimize the risk of complications associated with anesthesia, postoperative administration of meloxicam could be an alternative. Meloxicam and other NSAIDs are important drugs in pain management, and especially in multimodal analgesic protocols. The prolonged effect of meloxicam (24 hours) together with short acting opioids provides excellent postoperative analgesia in most cases (Polson et al., 2012). Ingwersen et al. (2012) also proves that pre-emptive use of meloxicam gives better pain management compared to postoperative administration. Preoperative use of meloxicam together with other analgesic agents will assist in a sufficient operative pain relief, reduce the dosage of anaesthetic agents and also prevent postoperative wind up. But to ensure a good post-operative analgesia, follow-up treatment is needed in most surgical patients. In Europe, meloxicam, ketoprofen and tolfenamic acid can be used postoperatively following the injection and provide a good analgesic efficacy after ovariohysterectomy (Slingsby and Waterman-Pearson, 2000; Iff, 2011). As an alternative for cats with increased risk of NSAID toxicity, buprenophine (Vetergesic) can be used. The drug can be administered sublingually, and will be absorbed by an oral transmucosal (OTM) pathway. The bioavailability will be 70%, and it will have an analgesic effect for 4-12 hours (average of 6 hours). The administration is user friendly for pet owners, and it has a good analgesic efficacy, which makes bupreorphine a good post-operative analgesic agent. It can be used alone or in combination with NSAIDs (Nyman, 2013).

Repeated use of meloxicam associated with acute pain, or relief of postoperative discomfort is licensed in Europe. Tolerance studies with repeated injections or oral application of meloxicam have been done to evaluate possible adverse events. At the licensed dose meloxicam did not give any renal or gastrointestinal side effects in cats treated 3 or 5 days post neutering (EPAR, 2012). In our study one cat classified into AKI stage 1 in the postoperative period. In these cases removal of the initiating factor is important. This cat did not receive any additional postoperative meloxicam, and no signs of renal disease developed. In a situation like this, lack of the postoperative meloxicam after surgery is crucial because the early stage renal disease (AKI 1) is not apparent clinically. But at the same time provision of postoperative analgesia should always be considered important, as it will decrease postoperative complications, increase animal welfare and time for wound healing. As discussed earlier, buprenorphine could be used as an alternative to NSAIDs to avoid renal toxicity. When applying meloxicam, another option could be to lower the licensed dosage of 0.05 mg/kg used post-operatively. Carroll et al. (2011) experienced good analgesic efficacy

when administering 0.025 mg/kg *per os* daily. Further reduction to 0.025 mg/ml oral suspension every second or third day may also provide sufficient analgesia in cats with chronic painful conditions (Lascelles *et al*., 2007). Based on the SARS report, adverse reactions were already reported at the oral dosage of 0.05 mg/kg (European Medicines Agency CVMP assessment report, 2006).

The chronic use of meloxicam in cats to relive pain associated with degenerative joint disease or other chronic disorders is on label in Europe, and off-label in the United States. Treatment of chronic pain in cats remains one of the most undertreated conditions in feline medicine, as it is both difficult to diagnose and there is limited amount of licensed products on the market suitable for cats. When used according to the licensed dose, meloxicam treated cats did not have increased incidences of acute renal failure compared to cats without any NSAID therapy (Gunew *et al*., 2008; Dammgen, 2007). Another study has challenged the long-term application safety by giving meloxicam to cats with existing chronic renal failure. The clinical study proved that meloxicam is safe to use in cats with existing chronic renal failure, as the cats receiving meloxicam had less progression in the renal disease compared to the control group (Gowan *et al*., 2011).

Both the European Medicine Agency and FDA (U.S. food and drug administration) have made reports, which with quantitative data, proves the theory of increased renal sensitivity in cats. A higher number of acute renal failure is reported in cats compared to dogs in connection with meloxicam administration. The uncertainty of the reports should however be taken into account, as they are less specific and does not consider individual differences in clinical state, anesthetic protocol or underlying diseases. When meloxicam is compared to other NSAIDs licensed for use in cats, it is proven to be equally efficient to provide post-operative analgesia (Slingsby and Waterman-Pearson, 2000). And to the authors' knowledge, none of the other NSAIDs are proven less nephrotoxic compared to meloxicam.

As a conclusion, NSAIDs are drugs with a narrow therapeutic index in cats, and should be used with caution. All cats receiving meloxicam should go through a physical examination, considering their hydration status, and have a basic biochemical analysis measuring blood urea nitrogen and creatinine. This study, together with previous research work supports the theory that if meloxicam is used according to labeled dose with appropriate patient monitoring and fluid therapy, minimal to no renal side effects should be expected. It could

suggest that the increased findings of renal toxicity could be associated with lack of patient selection, monitoring and postoperative care. The risk associated with meloxicam administration in concern for renal safety will still be a risk-benefit evaluation for each practitioner. But with a careful patient selection and a proper anesthetic protocol pre- and postoperative use of meloxicam in cats undergoing ovariohysterectomy would provide a sufficient and safe analgesia in most patients.

7. Summary

NSAIDs are frequently used analgesic agents in veterinary medicine. With anti-inflammatory, analgesic and antipyretic potential, in addition to prolonged duration of action NSAIDs are favorable drugs to use in animals. Although, a narrow therapeutic index in feline patients have resulted in a less frequent prescription of these drugs to cats, especially for long-term application. Pain is one of the most undertreated disorders among cats, because of their increased risk for drug toxicity. Meloxicam is a NSAID licensed by the European medicine agency for use in cats to relive postoperative, acute and chronic pain. In America, FDA does only approve meloxicam as a single injection, and there is no licensed NSAID for cats that can be used to relive chronic pain in the United States. The difference in the authorization is due to the increased risk of acute renal failure after repeated administrations of meloxicam in cats. A clinical study with 9 client owned cats was done to evaluate the renal safety of meloxicam in connection with ovariohysterectomy. The study was done to evaluate if there is a potential nephrotoxic effect of meloxicam in cats undergoing anesthesia, as a normotensive state is hard to achieve with most anesthetic agents. The cats received 0.3 mg/kg (5 mg/ml) meloxicam subcutaneously 10 minutes prior to surgery. A pre and postoperative blood analysis was done to evaluate creatinine and blood urea nitrogen levels. The renal safety was considered based on the blood analysis and clinical signs, and a classification of the renal disease was done according to the international renal society. The study did not revile any statistical significant results, and the trial was concluded negative. As a conclusion, meloxicam was considered safe when administered according to label dosage, and as long as appropriate patient selection, and pre and postoperative care was ensured.

8. Acknowledgments

9. Appendixes

9.1 Numerical rating scale (NRS) scoring system:

The evaluation adjusted for feline patients, and is based on position in cage, posture, reaction to wound palpation and pupil size. It is a subjective scoring system based on clinical observations.

0. Sternal/lateral recumbence in cage. Comfortable, not hiding. Normal posture when standing. No reaction to wound palpation. Pupils are normal.
1. Sternal/lateral recumbence in cage. Not hiding. Normal posture when standing. No/mild reaction to wound palpation. Pupils normal.
2. Sternal/lateral recumbence the cage. Not hiding. Normal posture when standing. Mild reaction to wound palpation. Pupils normal.
3. Sternal/lateral recumbence in cage. Might be hiding in cage. Hunched/normal posture when standing. Mild reaction to wound palpation. Pupils normal.
4. Sternal/lateral recumbence in cage. +/- vocalization. Hunched posture when standing. Reaction to wound palpation. Pupils normal.
5. Sternal/lateral recumbence in cage. +/- vocalization. Hunched posture when standing. Reaction to wound palpation. Pupils normal/dilated.
6. Recumbence/rolling in cage. +/- vocalization, hiding in cage. Arched back posture when standing. Reaction to wound palpation. Pupils normal/dilated.
7. Recumbence in cage/rolling in cage. Vocalization, hiding in cage. Arched back posture when standing. Reaction to wound palpation. Pupils dilated.
8. Rolling/uncomfortable in cage. Vocalization, hiding in cage. Arched back posture when standing. Reaction to wound palpation. Pupils dilated.
9. Rolling/paralyzed position in cage. Hiding in corner. Strong vocalization/no vocalization. Unwillingness to stand. Strong reaction to wound palpation. Dilated pupils.
10. Paralyzed position in cage, hiding in corner. Not able to stand. Strong reaction to wound palpation. Dilated pupils.

9.2 Statistical analysis values

The analysis was done using GraphPad Prism version 6 (GraphPad Software, Inc. www.graphpad.com).

Statistical analysis of creatinine results

	Preop.	Postop.
Number of values	9	9
Minimum	63	59
25% Percentile	72.5	74
Median	87	81
75% Percentile	105	114,5
Maximum	113	122
Mean	89.11	89.11
Std. Deviation	17.45	22.47
Std. Error of Mean	5.815	7.492
Lower 95% CI of mean	75.7	71.84
Upper 95% CI of mean	102.5	106.4
Lower 95% CI of median	71	74
Upper 95% CI of median	106	121
Sum	802	802

Statistical analysis of BUN results

	Preop.	Postop.
Number of values	9	9
Minimum	4.7	5.4
25% Percentile	7.25	7.15
Median	8.8	7.6
75% Percentile	9.45	8.65
Maximum	10.1	9.3
Mean	8.267	7.656
Std. Deviation	1.709	1.186
Std. Error of Mean	0.5696	0.3955
Lower 95% CI of mean	6.953	6.744
Upper 95% CI of mean	9.58	8.568
Lower 95% CI of median	6.4	7.1
Upper 95% CI of median	9.7	9.3
Sum	74.4	68.9

10. Bibliography

Alvaro-Gracia, J.M.: Licofelone – clinical update on a novel LOX/COX inhibitor for the treatment of osteoarthritis. *Rheumatology (Oxford)*. 43 (suppl. 1). p: 121-125.

Balmer, T.V., Irvine, D., Jones, R.S., et al. Comparison of carprofen and pethidine as postoperative analgesic in the cat. *Journal of Small Animal Practice*. 1998. Volume 39, Issue 4, pp. 158-164.

Baxter, K.: Advances in the management of acute kidney injury - proceeding. 2012. URL: http://canadawestvets.com/wp-content/uploads/2012/10/AdvancesManagementAcuteKidneyInjury.pdf. Accessed: 26.02.2013.

Benito-de-la-Víbora, J., Lascelles, B.D.X., García-Fernández, P., Freire, M., Gómez de Sengura, I.: Efficacy of tolfenamic acid and meloxicam in the control of postoperative pain following ovariohysterectomy in the cat. *Veterinary Anaesthesia and Analgesia*. 2008. Volume 35, Issue 6, pp. 501-510.

Blood, D.C., Studdert, V.P. and Gay, C.C.: Saunders Comprehensive Veterinary Dictionary third edition. Edinburgh, London, New York, Oxford, Philadelphia, St.Louis, Sydney, Toronto: Saunders Elsevier, 2007. p. 1245

Boehringer Ingelheim Vetmedica, Inc.: Metacam (meloxicam) package insertion. 2010. NADA 141-219. URL: http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/DrugLabels/UCM050397.pdf. Accessed: 14.5.2013.

Brander, G.C., Pugh, D.M., Bywater, R.J. and Jenkins, W.L.: Veterinary Applied Pharmacology & Therapeutic, 5th edition. London, Philadelphia, Toronto, Sydney, Tokyo: Baillière Tindall, 1991. p. 140-141.

Carroll, G.L., Howe, L.B. and Peterson, K.D.: Analgesic efficiency of preoperative administration of meloxicam or butorphanol in onychectomized cats. *J Am Vet Med Assoc*. 2005. 226, pp. 913-919.

Carroll, G.L., Narbe, R., Kerwin, S., Taylor, L., Petereson, K. and Hartsfield, S.M.: Dose range-finding study for the efficiency of meloxicam in cats utilizing a sodium urate-induced arthritis model. *Veterinary Anaesthesia and Analgesia*. 2011. Volume 38, Issue 4, pp. 394-406.

Chandrasekharan, N.V., Dai, H., Roos, K.L., Evanson, N.K., Tomsik, J., Elton, T.S. and Simmons, D.L.: COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. *Proceeding of the National Academy of Science of the U S A*. 2002. Volume 99, Issue 21, pp. 13926–13931. URL: http://www.pnas.org/content/99/21/13926.full.pdf+html. Accessed: 10.03.2013.

Coruzzi, G., Venturi, N., and Spaggiari, S.: Gastrointestinal safety of novel nonsteroidal anti-inflammatory drugs: selective COX-2 inhibitors and beyond. *Acta biomed*. 2007. Volume 78, Issue 2, pp. 96-110.

Cowgill, L.D.: IRIS grading of acute kidney injury. 2012. URL: http://rdoerfelt.ibk.me/data/downloads/226181/IRIS_20GRADING_20OF_20ACUTE_20KIDNEY_20INJURY-13_20Sept_202012.pdf. Downloaded: 09.06.2013

Dammgen, J.: The use of Metacam 0,5 mg/ml oral suspension in cats with osteoarthritis. *Metacam Symposium on Arthritis Diseases in Cats*. p: 19-20.

European Medicines Agency: EMEA/CVMP Assessment Report. Periodic safety update report (PSUR) on the use of oral formulations of Metacam in cats; covering the period 01 January 2003 - 15 October 2006 (Doc. Ref.: EMEA/CVMP/488412/2006).

European Medicines Agency: EMEA/CVMP Assessment Report. Periodic safety update report (PSUR) on the use of Metacam; covering the period 01 May 2007 - 30 April 2010 (Doc. Ref.: EMEA/CVMP/430797/2010).

EPAR (2010) Metacam European Public Assessment Report, scientific discussion. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/veterinary/000033/WC500065773.pdf. Accessed: 16.5.2013.

EPAR (2012) Metacam Eureopean Public Assessment Report. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/veterinary/000033/WC500065777.pdf. Accessed: 16.5.2013

FDA (U.S. food and drug administration): Freedom of information summary, supplemental new animal drug application 141-219. 2004. URL: http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118027.pdf. Accessed: 14.5.2013.

FDA (U.S. food and drug administration): FDA announces addition of boxed warning to Metacam (meloxicam) labels. 2010. URL: http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm231254.htm. Accessed: 14.5.2013.

FDA (U.S. food and drug administration): Adverse drug experience (ADE) report covering 1987 to April 30th 2013. Meloxicam. URL:http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM055409.pdf. Accessed: 20.05.2013

Flower, R.J. and Vane, J.R.: Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature (London)*. 1972. Volume 240, pp. 410-411.

Fox, M.S.: NSAIDs and beyond: the power of NSAIDs in the multimodal management of canine osteoarthritis. *Novartis Animal Health*. 2007. URL: http://www.hillsvet.com/conference-documents/Proceedings/Rehab_Symposium/3_The_Power_of_NSAIDs.pdf . Accessed 29.04.2013.

Giraudel, J.M., Diquelou, A., Laroute, V., Lees, P. and Toutain, P.L.: Pharmacokinetic/pharmacodynamic modelling of NSAIDs in a model of reversible inflammation in the cat. *British Journal of Pharmacology*. 2005. Volume 146, Issue 5, pp. 642-653.

Giraudel, J.M., Toutain, P.L. and Lees, P.: Development of in vitro assays for the evaluation of cyclooxygenase inhibitors and predicting selectivity of nonsteroidal anti-inflammatory drugs in cats. *American Journal of Veterinary Research*. 2005. Volume 66, Issue 4, pp. 700-709.

Giraudel, J.M., Toutain, P.L., King, J.N. and Lees, P.: Differential inhibition of cyclooxygenase isoenzymes in the cat by the NSAID robenacoxib. *Journal of veterinary pharmacology and therapeutics*. 2009. Volume 32, Issue 1, pp. 31-40.

Goodman, L.A., Brown, S.A., Torres, B.T., Reynolds, L.R. and Budsberg, S.C.: Effects of meloxicam on plasma iohexol clearance as a marker of glomerular filtration rate in conscious healthy cats. *American Journal of Veterinary Research*. 2009. Volume 70, pp. 826-830.

Gowan, R.A., Lingard, A.E., Johnston, L., Stansen, W., Brown, S.A. and Malik, R.: Retrospective case-control study of the effects of long-term dosing with meloxicam on renal function in aged cats with degenerative joint disease. *Journal of Feline Medicine and Surgery*. 2011. Volume 13, Issue 10, pp. 752-761.

Grudé, P., Guittarad, J., Garcia, G., Daoulas, I., Thoulon, F. and Ebner, T.: Excretion mass balance evaluation, metabolite profile analysis and metabolite identification in plasma and excreta after oral administration of [^{14}C] meloxicam to the male cat: preliminary study. *Journal of veterinary pharmacology and therapeutics*. 2010. Volume 33, Issue 4, pp. 396-407.

Gunew, M.N., Menrath, V.H. and Marshall, R.D.: Long-term safety and palatability of oral meloxicam at 0,01-0,03 mg/kg for treatment of osteoarhritic pain in cats. *Journal of Feline Medicine and Surgery*. 2008. Volume 10, pp. 235-241.

Harris, R.J.: Cyclooxygenase-2 inhibition and renal physiology. *Am J Cardiol*. 2002. Volume 89, 10D-17D.

Heeb, H.L., Chun, R., Koch, D.E., *et al*.: Single dose pharmacokinetics of piroxicam in cats. *Journal of veterinary pharmacology and therapeutics*. 2003. Volume 26, Issue 4, pp. 259-263.

Hewson, C.J., Dahoo, I.R. and Lemke, K.A.: Perioperative use of analgesics in dogs and cats by Canadian veterinarians in 2001. *Canadian Veterinary Journal*. 2006. Volume 47, pp. 352-359.

Iff, I. Non-steroidal anti-inflammatory drugs in dogs and cats – what's new? 2011. *Irish Veterinary Journal*. Volume 1, number 9, pp. 506-510.

Ingwersen, W., Fox, R., Cunningham, G. and Winhall, M.: Efficacy and safety of 3 versus 5 days of meloxicam as an analgesic for feline onychectomy and sterilization. *Canadian Veterinary Journal*. 2012. Volume 53, Issue 3, pp. 257-264.

IRIS: International Renal Interest Society. URL: http://www.iris-kidney.com/education/en/education01.shtml Accessed: 26.02.2013.

Jones, C.J. and Budsberg S.C.: Physiologic characteristics and clinical importance of the cyclooxygenase isoforms in dogs and cats. *JAVMA*. 2000. Volume 217, Issue 9, pp. 721-729.

Justus, C. and Quirke, J.F.: Dose-response relationship for the antipyretic effect of meloxicam in an endotoxin model in cats. *Veterinary research communications*. 1995. Volume 19, Issue 4, pp. 321-330.

Kamata, M., King, J.N., Seewald, W., Sakakibara, N., Yamashita, K. and Nishimura, R.: Comparison of injectable robenacoxib versus meloxicam for peri-operative use in cats: Results of randomised clinical trial. *The veterinary journal*. 2012. Volume 193, Issue 1, pp. 114-118.

Khan, S.A. and McLean, M.K.: Toxicology of frequently encountered nonsteroidal anti-inflammatory drugs in dogs and cats. *Veterinary clinics of North America Small Animals*. 2012. Volume 42, Issue 2, pp. 289-306.

Khan, K.N., Venturini, C.M., Bunch, R.T., *et al*.: Interspecies differences in renal localization of cyclooxygenase isoforms: implications in nonsteroidal anti-inflammatory drug-related nephrotoxicity. *Toxicol Pathol.* 1998. Volume 26, Issue 5, pp. 612-620.

Lascelles, B.D.X., Court, M.H., Hardie, E.M. and Robertson, S.A.: Nonsteroidal anti-inflammatory drugs in cats: a review. *Veterinary Anaesthesia and Analgesia*. 2007. Volume 34, pp. 228-250.

Lascelles, B.D., Cripps, P., Mirchandani, S., *et al*.: Carprofen as an analgesic for postoperative pain in cats: dose titration and assessment of efficacy in comparison to pethidine hydrochloride. *J Small Anim Pract*. 1995. Volume 36, Issue 12, pp. 535-541.

Lees, P., Taylor, P.M., Landoni, M.F., *et al*.: Ketoprofen in the cat: pharmacodynamics and chiral pharmacokinetics. *Vet Journal*. 2003. Volume 165, pp. 21-35.

Lees, P., Giraudel, J., Landoni, M. F., Toutain P. L.: PK–PD integration and PK–PD modelling of nonsteroidal anti-inflammatory drugs: principles and applications in veterinary pharmacology. *J. vet. Pharmacol. Therap*. 2004. Volume 27, Issue 6, pp. 491–502.

Lehr, T., Narbe, R., Jöns, O., Kloft, C. and Staab, A.: Population pharmacokinetic modelling and stimulation of single and multiple dose administration of meloxicam in cats. *Journal of veterinary pharmacology and therapeutics*. 2009. Volume 33, Issue 3, pp. 277-286.

Maddison, J.E.: Cats and NSAIDs – what are the issues? *Irish Veterinary Journal*. 2007. Volume 60, number 3, pp. 174-178.

Nyman, G.: Opioider for hund og katt – Ny viten (Opioids for dogs and cats – New knowledge). Conference by Horten Dyreklinikk and Orion Pharma Animal Health, Horten, Norway, 28.09.2013.

Papich, M.G.: An update on Nonsteroidal Anti-Inflammatory drugs (NSAIDs) in small animals. *Veterinary Clinics of North America: Small Animal practice*. 2008. Volume 38, Issue 4, pp. 1243-1266.

Polson, S., Taylor, M.P. and Yates, D.: Analgesia after feline ovariohysterectomy under midazolam-medetomidine-ketamine anaesthesia with buprenorphine or butorphanol, and carprofen or meloxicam: a prospective randomised clinical trial. *Journal of feline medicine and surgery*. 2012. Volume 14, Issue 8, pp. 553-559.

Ramsey I.: BSAVA Small Animal Formulary 7th edition. Gloucester: British Small Animal Veterinary Association, 2011, pp. 54, 216-217, 316-317, and 348-349.

Robertson, S.A., Taylor, P.M.: Pain management in cats – past, present and future. Part 1. The cat is unique. Part 2. Treatment of pain – clinical pharmacology. *Journal of Feline Medicine and Surgery*. 2004. Volume 6, Issue 5, pp. 313-333.

Robertson, S.A.: Managing pain in feline patients. *Veterinary Clinics of North America: Small Animal practice*. 2008. Volume 38, Issue 6, pp. 1267-1290.

Robson, M., Chew, D. and Aalst, S.: Intrinsic acute renal failure (ARF) associated with non-steroidal anti-inflammatory drugs (NSAID) use in juvenile cats undergoing routine desexing – 16 cases 1998-2005. *Journal of veterinary internal medicine*, 2006 ACVIM Abstracts. Volume 20, Issue 3, p. 740.

Schmid, V.B., Seewald, W., Lees, P. and King, J.N.: In vitro and ex vivo inhibition of COX isoforms by robenacoxib in the cat: a comparative study. *Journal of veterinary pharmacology and therapeutics*. 2010. Volume 33, Issue 5, pp. 444-452.

Slingsby, L.S. and Waterman-Pearson, A.E.: Postoperative analgesia in the cat after ovariohysterectomy by use of carprofen, ketoprofen, meloxicam or tolfenamic acid. 2000. *J Small Anim Pract*. Volume 41, Issue 10, pp. 447-450.

Sparkes, A.H., Heine, R., Lascelles, B.D.X., Malik, R., Sampietro, L.R., Robertson, S., Scherk, M. and Taylor, P.: ISFM and AAFP consensus guidelines, long-term use of NSAIDs in cats. *Journal of Feline Medicine and Surgery*. 2010. Volume 12, pp. 521-538.

Steagall, P.V., Taylor, P.M., Rodrigues, L.C., Ferreira, T.H., Minto, B.W. and Aguiar, A.J.: Analgesia for cats after ovariohysterectomy with either buprenorphine or carprofen alone or in combination. *Veterinary record*. 2009. Volume 164, Issue 12, pp. 359-363.